

Alkylation Reactions of Hydantoins and Succinimides

D. K. YUNG^{*▲}, T. P. FORREST[†], M. L. GILROY^{*}, and M. M. VOHRA[‡]

Abstract □ Five anticonvulsant agents, namely, diphenylhydantoin, mephentoin, ethotoin, ethosuximide, and phensuximide, and a number of other hydantoins were investigated in their reactions with *p*- and *m*-nitrobenzyl bromides in the presence of sodium carbonate. The structures of the alkylation derivatives and other products formed in the reactions were studied. On the basis of the melting points of the alkylation derivatives, it was possible to identify and differentiate the five anticonvulsants. 3-*p*-Nitrobenzyl-5,5-diphenylhydantoin, *N*-*p*-nitrobenzyl-2-ethyl-2-methylsuccinimide, and 3,3'-diethyl-5,5'-diphenylhydantoin, at a dose of 1 g./kg. given orally, provided no protection against pentylenetetrazol-induced seizures in mice.

Keyphrases □ Hydantoins and succinimides—alkylation with nitrobenzyl bromides, anticonvulsant properties of products □ Succinimides and hydantoins—alkylation with nitrobenzyl bromides, anticonvulsant properties of products □ Anticonvulsants—alkylation reactions of hydantoins and succinimides □ Alkylation reactions—hydantoins and succinimides

Many substituted hydantoins and succinimides are anticonvulsants. For identification purposes, some of these chemical compounds, namely, diphenylhydantoin (I), mephentoin (II), ethotoin (III), ethosuximide (IV), and phensuximide (V), were treated with nitrobenzyl bromides in the presence of a weak base to form crystalline alkyl derivatives. There are several possible structures available for these alkyl derivatives, because alkylation could occur at more than one site in the hydantoin and succinimide molecules. This study reports on the structures of the alkylation derivatives and other products formed in the reactions.

EXPERIMENTAL¹

5-Phenylhydantoin—This compound was obtained from benzaldehyde, ammonium carbonate, and potassium cyanide *via* the Bucherer-Berg reaction. The yield was 86%, m.p. 180.5–182° [lit. (1) m.p. 179°].

5-Ethyl-5-phenylhydantoin—This compound was obtained from propiophenone, ammonium carbonate, and potassium cyanide *via* the Bucherer-Berg reaction. The yield was 69%, m.p. 199° [lit. (2) m.p. 199°].

3-Methyl-5,5-diphenylhydantoin—The procedure reported by Dudley and Bius (3) was followed. The yield was almost quantitative, m.p. 214–215.5° [lit. (4) m.p. 213–214°].

General Procedure for Alkylation Reactions—A solution of the alkylating agent (0.01 mole) in 60 ml. of ethanol was added to a mixture of a hydantoin or succinimide (0.01 mole), sodium carbonate (0.02 mole), and 30 ml. of water. The reaction mixture was stirred under reflux for 1.5 hr. and cooled. The alkylated products were then isolated by one of the following three methods. The physical constants for the alkylated products prepared together with the recrystallization solvent are summarized in Tables I and II.

Method A—The material that separated from the reaction mixture after cooling was collected by filtration and washed thoroughly

with water to yield the crude product. Alkyl derivatives isolated by this method were 3-*p*-nitrobenzyl-5,5-diphenylhydantoin (VI), 3-*m*-nitrobenzyl-5,5-diphenylhydantoin (VII), 3-*p*-nitrobenzyl-5-ethyl-5-phenylhydantoin (VIII), and 3,3'-bis(*p*-nitrobenzyl)-5,5'-diphenylhydantoin (IX).

Method B—After the cooled reaction mixture was filtered, water was added to the filtrate until cloudiness occurred. On cooling, a solid precipitated which was collected by filtration to give the crude product. Alkyl derivatives obtained by this method were 1-*p*-nitrobenzyl-3-methyl-5-ethyl-5-phenylhydantoin (X), 1-*p*-nitrobenzyl-3-methyl-5,5-diphenylhydantoin (XI), *N*-*p*-nitrobenzyl-2-ethyl-2-methylsuccinimide (XIV), *N*-*m*-nitrobenzyl-2-ethyl-2-methylsuccinimide (XV), and *N*-methyl-2-phenyl-2-*p*-nitrobenzylsuccinimide (XVI).

Method C—After the reaction mixture was filtered, the ethanol in the filtrate was distilled off to leave behind a brownish oily residue in the aqueous solution. The residue was separated and triturated with a small amount of methanol to yield the crude product. Alkyl derivatives obtained by this method were 3-ethyl-5-*p*-nitrobenzyl-5-phenylhydantoin (XII) and 3-ethyl-5-*m*-nitrobenzyl-5-phenylhydantoin (XIII).

The precipitate that separated from the reaction mixture when III was used yielded 2.2 g. (54%) of 3,3'-diethyl-5,5'-diphenylhydantoin (XVII), m.p. 328–330° [lit. (3) m.p. 326–328°].

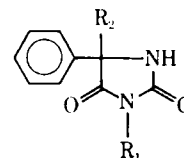
4,4'-Dinitrobenzyl (XVIII)—This compound was obtained by reacting *p*-nitrobenzyl bromide (0.02 mole) with III (0.01 mole) in the presence of sodium carbonate under the conditions described for alkylation reactions. The crude product was collected from the cooled reaction mixture and washed with water. One recrystallization from ethanol and acetone gave 1 g. (35%) of pure 4,4'-dinitrobenzyl (XVIII), m.p. 179.5–181° [lit. (5) m.p. 179–180°].

Acute Toxicity—The compound was suspended in 10% aqueous acacia and administered orally to male albino mice (20–30 g.) at a dosage of 2 g./kg. The mice were observed over 3 days.

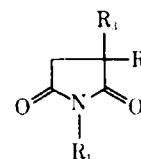
Antipentylenetetrazol Activity—The procedure of Swinyard *et al.* (6) was followed. The amount of pentylenetetrazol used for challenge was 85 mg./kg. and was given subcutaneously 2 hr. prior to the oral administration of the test compound.

RESULTS AND DISCUSSION

Reaction of diphenylhydantoin (I), obtained commercially, with *p*-nitrobenzyl bromide in the presence of sodium carbonate gave a crystalline alkyl derivative in 82% yield. Theoretically, alkylation could occur on the nitrogen atoms of the 1- and 3-positions and on the oxygen atoms of the 2- and 4-positions. Thus, the alkyl derivative of I could be VI, 1-*p*-nitrobenzyl-5,5-diphenylhydantoin (XIX), 2-*p*-nitrobenzoxy-4,4'-diphenyl-2-imidazolin-5-one (XX), 2-*p*-ni-



- I: R₁ = H, R₂ = C₆H₅
II: R₁ = CH₃, R₂ = CH₂CH₃
III: R₁ = CH₂CH₃, R₂ = H



- IV: R₁ = H, R₂ = CH₃, R₃ = CH₂CH₃
V: R₁ = CH₃, R₂ = H, R₃ = C₆H₅

¹ Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Elemental analyses were performed by Dr. F. B. Strauss, Microanalytical Laboratory, Oxford, England. The IR spectra were recorded on a Perkin-Elmer model 237B spectrophotometer in potassium bromide. A Varian model T-60 spectrometer was used to record the NMR spectra, with deuterated chloroform as solvent and tetramethylsilane as the internal reference.

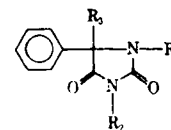


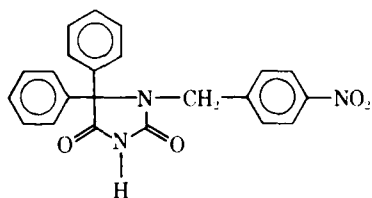
Table I—Alkyl Derivatives of Hydantoin

Compound	R ₁	R ₂	R ₃	Yield, %	Melting Point	Re-crystallization Solvent	Formula	Analysis, %	Calc.	Found
VI	H	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂	C ₆ H ₅	82	181–183°	Ethanol	C ₂₂ H ₁₇ N ₃ O ₄	C 68.21 H 4.43 N 10.85	67.92 4.32 10.72	
VII	H	<i>m</i> -NO ₂ C ₆ H ₄ CH ₂	C ₆ H ₅	93	191.5–192.5°	Ethanol	C ₂₂ H ₁₇ N ₃ O ₄	C 68.21 H 4.43 N 10.85	68.16 4.42 10.85	
VIII	H	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂	CH ₃ CH ₂	76	175–176°	Acetone-ethanol	C ₁₈ H ₁₇ N ₃ O ₄	C 63.71 H 5.05 N 12.38	63.82 5.37 12.16	
IX ^a	—	—	—	32	312–315°	Pyridine	C ₃₂ H ₂₄ N ₆ O ₈	C 61.93 H 3.90 N 13.54	61.89 4.00 13.38	
X	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂	CH ₃	CH ₃ CH ₂	34	126–127°	Ethanol-water	C ₁₉ H ₁₉ N ₃ O ₄	C 64.58 H 5.42 N 11.89	64.21 5.59 11.86	
XI	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂	CH ₃	C ₆ H ₅	20	194–195.5°	Ethanol-water	C ₂₃ H ₁₇ N ₃ O ₄	C 68.82 H 4.77 N 10.47	68.72 4.90 10.47	
XII	H	CH ₃ CH ₂	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂	9	185.5–187°	Methanol-ether	C ₁₈ H ₁₇ N ₃ O ₄	C 63.71 H 5.05 N 12.38	63.61 5.15 12.12	
XIII	H	CH ₃ CH ₂	<i>m</i> -NO ₂ C ₆ H ₄ CH ₂	9	145–146°	Methanol-ether	C ₁₈ H ₁₇ N ₃ O ₄	C 63.71 H 5.05 N 12.38	63.88 5.11 12.31	

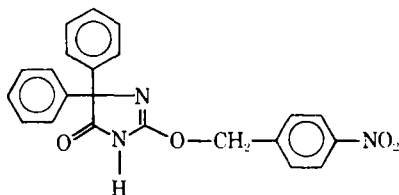
^a Compound IX is 3,3'-bis(*p*-nitrobenzyl)-5,5'-diphenylhydantoin. See text for structure.

trobenzoxo-5,5-diphenyl-2-imidazolin-4-one (XXI), or 4-*p*-nitrobenzoxo-5,5-diphenyl-3-imidazolin-2-one (XXII). Chatten and Levi (7), in their study of the reaction of barbiturates with the same alkylating agent and under the same conditions, postulated that alkylation took place on the C-4 and C-6 oxygen atoms of the barbiturate molecule.

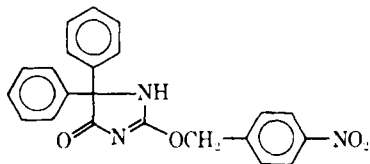
Results of IR studies on I and the reaction product showed that



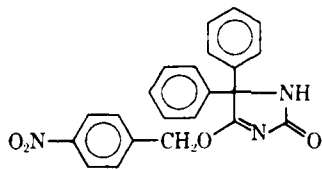
XIX



XX



XXI



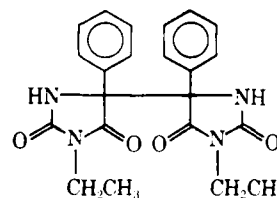
XXII

the oxygen atoms of the 2- and 4-positions were not involved in the alkylation of I. In both IR spectra, two carbonyl peaks were observed at 1770 and 1718 cm⁻¹, indicating that alkylation could not have occurred on the oxygen of the 2- or 4-position (8). Consequently, the alkyl derivative of I could only be VI or XIX.

The NH absorption bands of I and its alkylation product were not well resolved enough in the 3315–3220-cm⁻¹ region to permit a reliable structural assignment to the alkylation product. However, since the UV absorption maximum of the alkyl derivative was not shifted in alkaline solution, and in view of the report by Stuckey (9) that only hydantoin having a hydrogen atom at the 3-position showed a shift in the absorption maximum, it would appear that the alkyl derivative of I was VI and not XIX.

To demonstrate that the nitrogen atom of N-3 in I was indeed the more reactive site for alkylation, 3-methyl-5,5-diphenylhydantoin was treated with *p*-nitrobenzyl bromide using the same conditions as with I. As expected, the reaction proceeded much more slowly. About 81% of the starting hydantoin was recovered. Only a 20% yield of a crystalline product was isolated, and this product was identified as 1-*p*-nitrobenzyl-3-methyl-5,5-diphenylhydantoin (XI) by IR and NMR data (Table III). The reaction of I with the same bromide gave no corresponding N-1 alkyl derivative. Examination of the IR spectrum of the parent hydantoin showed that there were one sharp and intense NH band at 3315 cm⁻¹ and two prominent carbonyl bands in the 1775–1690-cm⁻¹ region. The spectrum of XI contained two carbonyl bands and two aromatic nitro bands but no NH band at 3315 cm⁻¹. The disappearance of the NH absorption band indicated that the crystalline reaction product was indeed XI.

Similar results were observed in the reaction of II. There was a 34% yield of the alkylation product 1-*p*-nitrobenzyl-3-methyl-5-ethyl-5-phenylhydantoin (X), whose IR spectrum contained no NH-



XVII

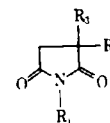
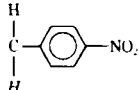
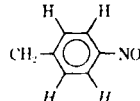


Table II Alkyl Derivatives of Succinimides^a

Compound	R ₁	R ₂	R ₃	Yield, %	Melting Point	Formula	Analysis, %	
							Calc.	Found
XIV	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂	CH ₃ CH ₂	CH ₃	40	112.5–113.5°	C ₁₄ H ₁₆ N ₂ O ₄	C 60.86 H 5.83 N 10.14	61.14 5.80 10.38
XV	<i>m</i> -NO ₂ C ₆ H ₄ CH ₂	CH ₃ CH ₂	CH ₃	51	65.5–67°	C ₁₄ H ₁₆ N ₂ O ₄	C 60.86 H 5.83 N 10.14	60.86 5.85 9.97
XVI	CH ₃	C ₆ H ₅	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂	31	137.5–139°	C ₁₈ H ₁₆ N ₂ O ₄	C 66.65 H 4.97 N 8.64	66.54 5.16 8.66

^a The recrystallization solvent for these derivatives was ethanol.

Table III- NMR Chemical Shifts^a in Deuteriochloroform

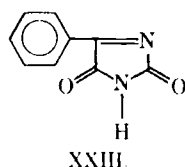
Compound	N—H		
VI	7.16 (s)	4.76 (s)	8.14 7.48 (AB) <i>J</i> _{AB} = 8 Hz.
VIII	6.56 (s)	4.74 (s)	8.13 7.47 (AB) <i>J</i> _{AB} = 8 Hz.
XIV	—	4.71 (s)	8.14 7.45 (AB) <i>J</i> _{AB} = 8 Hz.
XII	7.85 (s)	3.62 3.32 (AB) <i>J</i> _{AB} = 13 Hz.	8.00 7.28 (AB) <i>J</i> _{AB} = 8 Hz.
XVI	—	3.30 3.56 (AB) <i>J</i> _{AB} = 13 Hz.	8.05 7.20 (AB) <i>J</i> _{AB} = 8 Hz.
X	—	4.62 4.18 (AB) <i>J</i> _{AB} = 15 Hz.	8.05 7.32 (AB) <i>J</i> _{AB} = 8 Hz.
XI	—	4.70 (s)	7.85 6.86 (AB) <i>J</i> _{AB} = 8 Hz.

^a Parts per million.

stretching absorption. About half of II was recovered unreacted. When 5-ethyl-5-phenylhydantoin was used, the expected N-3 alkylation product, 3-*p*-nitrobenzyl-5-ethyl-5-phenylhydantoin (VIII), was isolated in 76% yield.

The reaction of III with *p*-nitrobenzyl bromide in equimolar concentration was complicated by the fact that III dimerized in alkaline solution to form 3,3'-diethyl-5,5'-diphenylhydantoin (XVII) in 54% yield. In addition to this dimer, about a 9% yield of the alkylation product 3-ethyl-5-*p*-nitrobenzyl-5-phenylhydantoin (XII) was also isolated. The IR spectrum of XII showing strong NH, carbonyl, and aromatic nitro absorption bands was in agreement with the assigned structure. The chemical shift of the benzylic methylene group is consistent with its attachment at a carbon rather than a nitrogen atom. Therefore, it seems reasonable that alkylation has occurred at the 5-position and not at the 1-position of III.

Dimerization of similar hydantoin molecules has been reported in the literature. Edward and Nielsen (10) reported that, in aqueous alkali at room temperature, 5-phenylhydantoin absorbed molecular oxygen to give 5,5'-diphenylhydantoin. These workers speculated that the reaction probably involved the oxidation of the carbanion of 5-phenylhydantoin to 5-hydroxy-5-phenylhydantoin which, in the form of the pseudobase (XXIII), condensed with a second molecule of 5-phenylhydantoin to yield the product. For this reason, in two separate experiments the reaction of III with the nitrobenzyl bromide was carried out under nitrogen to determine if the formation of XVII could be prevented. However, in both cases the dimer

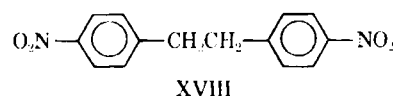


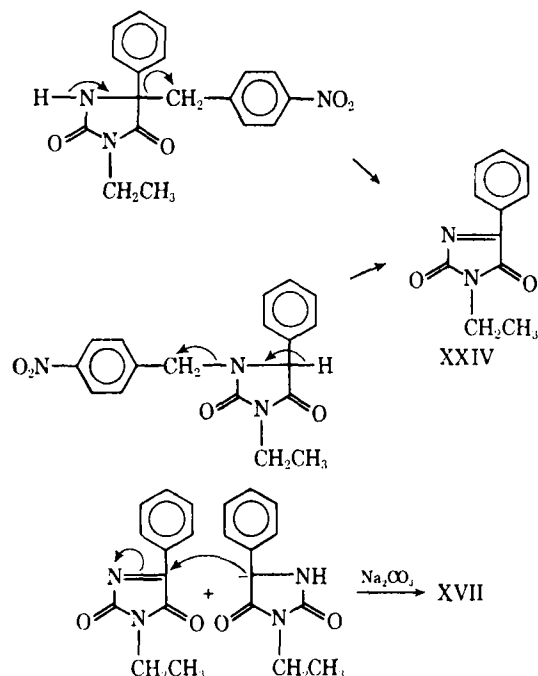
was still the major product and the yield of XII was in no way increased.

In another attempt to increase the yield of XII, III was treated with two equivalents of *p*-nitrobenzyl bromide. The reaction under these conditions gave the similar percent yield of XII, but there was no formation of XVII. Instead, the major product, in 35% yield, was 4,4'-dinitrobenzyl (XVIII). The identity of XVIII was confirmed by comparison of its melting point, mixed melting point, and IR spectrum with an authentic sample. The formation of XVIII was totally unexpected. Reaction of sodium carbonate and *p*-nitrobenzyl bromide without III did not give any XVIII. It appears that the hydantoin molecule has an important role to play in the production of XVIII.

The formation of the hydantoin dimer XVII as the major product when *p*-nitrobenzyl bromide was used in equimolar quantity and the formation of the reagent dimer XVIII when the alkylating agent was in excess raised interesting questions. Since carrying out the alkylation reaction in a nitrogen atmosphere did not stop the production of XVII, it seems that air oxidation is not the mechanism of formation in the presence of *p*-nitrobenzyl bromide. A plausible mechanism could involve the elimination of the stabilized benzylic carbanion from the 1- or 5-alkylated derivative to form the pseudobase XXIV. The dimer could then be formed by reaction of the carbanion and XXIV (Scheme I).

The formation of the reagent dimer XVIII when there was an excess of *p*-nitrobenzyl bromide could have been caused by the rearrangement of the dialkyl derivative 1,5-bis(*p*-nitrobenzyl)-3-ethyl-5-phenylhydantoin (XXV) (Scheme II). Such a rearrangement



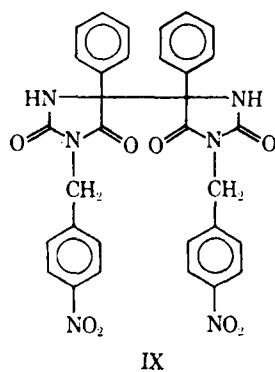


Scheme I—Proposed mechanism for the formation of 3,3'-diethyl-5,5'-diphenylhydantil (XVII)

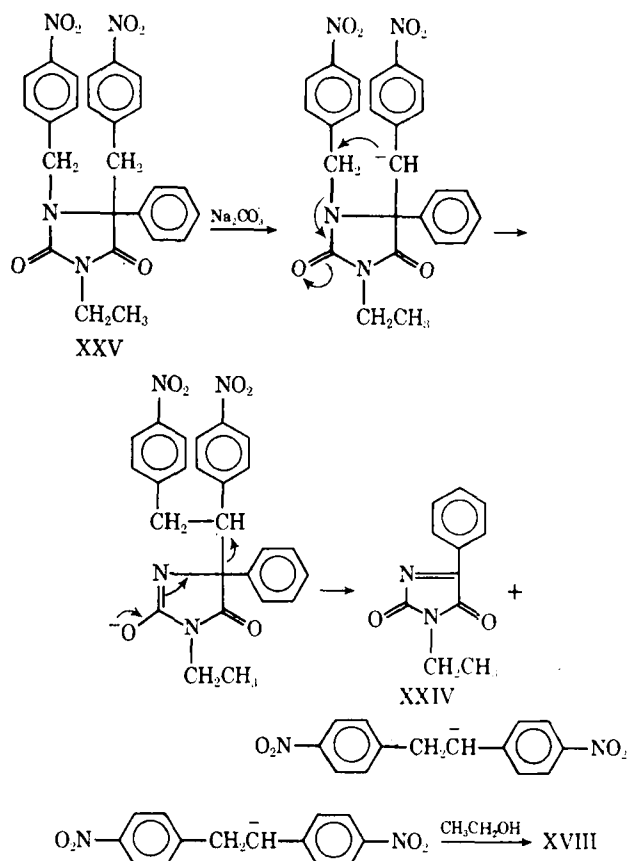
requires that the benzylic protons be acidic, as would be the case in the *p*-nitro derivative but not the *meta*-isomer. Such a mechanism is supported by the fact that alkylation of III with *m*-nitrobenzyl bromide under similar conditions did not produce the analogous 3,3'-dinitrobenzyl. The hydantoin dimer XVII and the alkyl derivative 3-ethyl-5-*m*-nitrobenzyl-5-phenylhydantoin (XIII) were the two products isolated.

The interesting formation of XVII and XVIII prompted the study of 5-phenylhydantoin in the same manner as III. When 5-phenylhydantoin was allowed to react with *p*-nitrobenzyl bromide in a 1:1 ratio, only the dimer of the N-3 alkylated derivative 3,3'-bis-(*p*-nitrobenzyl)-5,5'-diphenylhydantil (IX) was isolated in 32% yield. However, when 5-phenylhydantoin was treated with the nitrobenzyl bromide in a 1:2 ratio, IX and XVIII were obtained in 20 and 45% yields, respectively.

On the basis of the results obtained, a general statement can be made on the alkylation pattern of the hydantoin molecule in a weak base medium. Alkylation occurs at the 1-, 3-, and 5-positions but not at the 2- and 4-positions of the molecule. The 3-position is most reactive and is always the major site for alkylation. Alkylation at the 1-position occurs less readily than alkylation at the 5-position when there is a phenyl substituent on the 5-position. When both the 3- and 5-positions are blocked, N-1 alkylation can take place. If the 3-position is substituted and the 1- and 5-positions are both available, the formation of a hydantoin dimer is highly possible in the presence of air or when *p*-nitrobenzyl bromide is used as the alkylat-



IX



Scheme II—Proposed mechanism for the formation of 4,4'-dinitrobenzyl (XVIII)

ing agent. If the 3-position is also available, then an N-3 alkylated hydantoin dimer is obtained.

The reactions of the succinimides IV and V with *p*-nitrobenzyl bromide were straightforward. *N*-*p*-Nitrobenzyl-2-ethyl-2-methylsuccinimide (XIV) was obtained in 40% yield, and its identity was confirmed by IR and NMR spectra.

When V was treated with *p*-nitrobenzyl bromide, a 31% yield of a bright-orange reaction product was isolated. The IR spectrum showed the presence of two carbonyl groups and an aromatic nitro grouping. The chemical shift of the protons in the NMR spectrum indicated that the *p*-nitrobenzyl substituent was attached at the 2-position. Thus, the colored reaction product was identified as *N*-methyl-2-phenyl-2-*p*-nitrobenzylsuccinimide (XVI). Like II, there was no reaction between V and *m*-nitrobenzyl bromide.

The alkylation products of I-V with *p*- and *m*-nitrobenzyl bromides are crystalline compounds with sharp and reproducible melting points. Therefore, these products can be used as derivatives for identification and differentiation. As indicated in Tables I and II, the five anticonvulsant drugs studied can be identified and differentiated on the basis of the melting points of these derivatives. Unfortunately, the usefulness of the *p*- and *m*-nitrobenzyl derivatives in identifying or differentiating III from the other four hydantoins appears to be limited because the derivatives could only be obtained in low yields.

The reaction procedures developed for the pure drugs were successfully applied to the various dosage forms of I, II, IV, and V. To have a workable quantity of products, at least 250 mg. of drug in the sample was required. It was also observed that if a sodium salt was used in the formulation, the salt had to be first neutralized with dilute hydrochloric acid to yield the free acid; the free acid was then redissolved in sodium carbonate solution for the alkylation reaction. The aqueous solution of sodium diphenylhydantoin, when allowed to react directly with *p*-nitrobenzyl bromide, produced an almost quantitative yield of *trans*-4,4'-dinitrostilbene, m.p. 290–292° [lit. (11) m.p. 289.5–291°]. In a solution of this basicity, *p*-nitrobenzyl bromide can be ionized to form the carbanion, which displaces the bromide from another molecule of the alkylating agent. The stilbene

was believed to have been formed after elimination of hydrobromide from this displacement intermediate.

Samour *et al.* (12) reported that some alkoxymethyl derivatives of I were effective anticonvulsants. Therefore, it was of interest to test some alkyl derivatives for anticonvulsant activity. Three compounds representing three different chemical structures were studied. Results of the biological testings showed that VI, XIV, and XVII, when suspended in 10% acacia and given orally, exhibited no activity against pentylenetetrazol-induced seizures in mice at a dose of 1 g./kg. According to the acute toxicity studies, these compounds appeared to be relatively nontoxic. None of the animals died as a result of oral administration at a 2-g./kg. dose level, which was the maximum amount of the compound that could be suspended in an appropriate volume of 10% acacia.

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▲ To whom inquiries should be directed.

Kinetics and Factors Affecting Stability of Methylprednisolone in Aqueous Formulation

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Abstract □ An investigation was made of the factors affecting the rate of degradation of methylprednisolone solubilized by polysorbate 80 in an aqueous formulation containing polar additives and a sequestering agent as a function of temperature at pH 4.6 and 5.1. The presence of polar additives decreased the apparent solubility of methylprednisolone in one formulation at pH 4.6 and 25°. However, since methylprednisolone was in solution, but not within the polyoxyethylene exterior of the polysorbate 80 micelles, it degraded at a faster rate. By selecting the proper concentration of polysorbate 80 and adjusting to the same pH of 4.6 in another formulation, the autoxidative degradation rate of the primary alcoholic group at C-21 was reduced to approximately half even in the presence of oxygen. The increase in stability was also evident

from the increase of the apparent activation energy from 18.2 to 23.1 kcal./mole. The mechanism of solubilization and stabilization based on hydrogen bonding and inclusion into the polyoxyethylene exterior of the polysorbate 80 micelles is proposed.

Keyphrases □ Methylprednisolone aqueous formulations—effect of polysorbate 80 solubilization on stability, mechanism, kinetics □ Polysorbate 80—effect on methylprednisolone stability in aqueous formulations, mechanism of solubilization □ Solubilization, methylprednisolone—effect of polysorbate 80 on stability in aqueous formulations, mechanism, kinetics □ Stabilization of methylprednisolone in aqueous formulations—polysorbate 80 solubilization

In the pharmaceutical field, the phenomenon of micellar solubilization of drugs in aqueous solutions of surfactants is used not only for solubilizing the drug but also for protecting against degradative processes such as hydrolysis and autoxidation. The stabilization of esters against alkaline hydrolysis in aqueous solutions containing nonionic, cationic, and anionic surfactants has been reported (1–3). Vitamin A alcohol solubilized in an aqueous nonionic surfactant solution was reported (4) to be more stable to autoxidation than vitamin A solubilized in cottonseed oil. Similarly, vitamin A alcohol solubilized in aqueous nonionic

surfactant solution containing 30% (w/v) glycerin was more stable to autoxidation than vitamin A solubilized in arachis oil (5).

Nonionic surfactant polysorbate 80 (polyoxyethylene 20 sorbitan monooleate) increased the solubility and the stability of methylprednisolone in aqueous solutions prepared by heating between 40° and the decomposition point (6). However, the quantitative data regarding the extent of stabilization of methylprednisolone were not presented (6).

This article deals with the factors affecting the chemical stability of methylprednisolone solubilized by